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DANN, DORFMAN, HERRELL & SKILLMAN
1601 MARKET STREET
SUITE 2400
PHILADELPHIA, PA 19103-2307

EXAMINER	
GEMENIANO, MALOU C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/750,748	TENNEKOON ET AL.	
	Examiner	Art Unit	
	Malou C. Gemeniano	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/02/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

Applicant claims domestic priority under 35 USC 119(e) to US Application 09/833066 filed on 4/12/2001, which claims the benefit of US Provisional Application No. 60/196473, filed 4/12/2000 and US Provisional Application No. 60/387,267, file 6/7/02 that has been abandoned; therefore, the current application 10/750748 is given the priority date of 4/12/2000. As noted, claims 1-14 are cancelled. The following detailed action is an examination of pending claims 15-24.

The use of the trademark MATRIGEL has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 18 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6673606. Although the conflicting claims are not identical, they are not patentably distinct from each other because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 18 is generic to all that is recited in claims 1-4 of US Patent no. 6673606. That is, claims 1-4 of US Patent no. 6673606 fall entirely within the scope of claim 18 or, in other words, claim 18 is anticipated by claims 1-4 of US patent 6673606. Specifically both set of claims encompass methods for differentiating MSCs cells into neurons or oligodendrocytes in vitro. The present claim is method of differentiating MSCs cells by exposing cells to an unspecified condition such that the MSC cells differentiated into neurons or oligodendrocytes. The claims of US Patent No. 6673606 are specific for the method of differentiating MSC cells into specifically oligodendrocytes wherein the cells are exposed specifically to a neuroblastoma conditioned medium wherein B104 is the said conditioned medium. Accordingly, the method of differentiating MSC using the specific neuroblastoma medium is encompassed by claim 18.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15-18 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification, while being enabling for

A method for differentiating a mesenchymal stromal cell into an oligodendrocyte precursor cell, comprising (i) providing a composition in vitro that consists essentially of said mesenchymal stromal cells and a physiological compatible carrier (ii) and culturing said cells in a medium comprising a neuroblastoma conditioned medium, wherein culturing step provided oligodendrocytes precursor cells capable of differentiating into oligodendrocytes; the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or so broad of a subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method for treating a pathology characterized by damaged myelin or neurological deterioration, comprising (i) providing a composition in vitro that consists essentially of mesenchymal stromal cells and physiologically compatible carrier thereof, (ii) exposing said composition to conditions such that said mesenchymal stromal cells or oligodendrocyte precursor cells differentiate into differentiated cells of a types selected from neuron and oligodendrocyte, and (iii) allowing cells to compensate for said neurological deterioration or damaged myelin in a subject suffering from said pathology. The instant claims

are also drawn to a method for preparing differentiated cells consisting essentially of any species MSC cells and any physiologically compatible carrier and exposing said cells to any condition such that said MSC differentiate into neurons or oligodendrocytes.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention/ breadth of the claim

The present invention is drawn to a method of treating a large genus of pathologies or diseases related to damaged myelin or neurological deterioration by providing to a large genus of subjects suffering from said pathology any large genus of composition that comprises mesenchymal stromal cells and any physiological compatible carrier wherein the method comprises culturing said cells in unspecified conditions such that the said cells differentiate from mesenchymal stromal cells or oligodendrocyte precursor cells such that the said cells compensate for said damaged myelin or neurological deterioration. The specification describes that in diseases such as Parkinson's disease the neurons are not replaced upon their loss and in diseases such as multiple sclerosis, the breakdown in axonal sheathing of are not replaced. The claims are drawn to induce and differentiate human mesenchymal stromal (MCSs) cells into

oligodendrocyte precursors cells capable of differentiating into oligogodendrocytes and neurons. The Applicant sets forth a notion that oligodendrocytes precursor derived form MCSs can be used as a therapeutic source for neurotransplantation with regards to the treatment and replacement of damaged myelin or compensation of neurological deterioration.

However, the claims when given the broadest reasonable interpretation encompass a method of administering any composition to subjects suffering from pathologies related to myelin deterioration or neurological deterioration wherein the composition comprises mesenchymal stromal cells and any physiological compatible carrier wherein the method comprises culturing said cells in unspecified conditions such that the said cells differentiate from mesenchymal stromal cells or oligodendrocyte precursor cells such that the said cells compensate for said damaged myelin or neurological deterioration. The claims also broadly encompass any unspecified method for the differentiation of MCS cells by culturing said MCS cells in any condition such that said cells differentiate in vitro into neurons or oligodendrocytes.

Specific considerations for *in vivo* stem cell therapy such as *systemic barriers* have to be addressed for an *in vivo* cell therapy method of preventing a human disorder disease associated with neuronal cell death. As such the specification lacks any description regarding the method (route, vectors types, dosage, patient profile) of preventing a human disorder disease associated with damaged myelin or neurological deterioration therefore, the broad aspects of stem cell therapy composition to treat any human disorder relating to myelin damaged and or neurological deterioration is not reasonably enable for the full scope embraced by the claims.

The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the

invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed application.

State of the prior art

The instant invention is drawn to a nature of effective treatments for CNS pathologies characterized by neuron loss, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and stroke as well as provide treatments for metabolic lipid storage disease, such as Tay-Sachs, Gm1 gangliosidosis, adrenoleukodystrophy, Krabbe's disease, metachromatic leukodystropy and multiple sclerosis, which involve oligodendrocytic loss. In addition, the instant invention also provided for the use of MSCs and MSC-differentiated cell to amerliorate the neuronal loss brought on by head injury or other trauma wherein the method comprises providing a composition of MSC cells to said subject suffering from such pathologies, wherein the said MSC cells are differentiated in vitro into oligodendrocytes and neurons whereby the differentiated cells are allowed to compensate for neurological deterioration and damaged myelin in a subject. Taking the broadest interpretation of the claims would encompasse the in vivo stem cell therapy treatment in humans.

However, at the time of filing, related art is considered unpredictable. The following reference have been cited herein to illustrate the state of art related to the treatment of demyelinating disease, Eglitis et al. (PNAS 1997 94(8) p. 4080-4085) teaches that although many neurotrophic factors show promise in the treatment of CNS disorders, their use has been hindered by their ability to cross the blood-born barrier and by their limited diffusion in CNS tissue. In addition adverse effects have been reported after systemic administration of some neurotrophins. Using marrow-derived cells to deliver therapeutic proteins directly to the site of

CNS pathology may be more benign than systemic adminstration of toxic molecule (see p. 4085, Last ¶). In support of this unpredicatibilty in the art, Isacson et al. (The Lancet Neurology p. 417-424) teaches that novel cell-based therapies have been approached, understandably, with caution by the neurology community and that stem cell are a potential of source of specific neurons or support cells that could regenerate synapses and repair biofeedback circuits. However, the selection and design of specific cells for transplantation therapies has not been extensively investigated (see p. 417 1st ¶). In regards to certain cell-transplantation therapies, the outcome of double-blind trials was mixed and primary endpoints were not fully met. Various factors should be considered such as side-effects, the important of patient selection on the basis of preoperative assessment of drug responsiveness, disease severity and disease stage (p. 418 2nd ¶). Furthermore, Isacson described that certain cell therapies have been able to allow patients eliminate their dopamine-replacement medication altogether. However, such cases are rare and the optimum parameters for selection of patients are not well understood. For those patients who have received cell transplants, why some transplants work, and other do not is still unclear (see p. 422 Last ¶). Lastly, Vogel et al (Science 2000, vol 290 no. 5497 p. 1672) further exemplifies the unpredictability of stem cell therapies or transplants and cautions researchers to interpret the results. Vogel et al questions, "can the dramatic finding that so far have grown out of work with stem cells take form mice be repeated in human? Human cells grow more slowly and divide less often in culture than their mouse counterparts. And human stem cells are proving decidedly less predictable. Any human treatments, suffice it to say, are years away" (p. 1673). The totality of the cited references exemplifies the potential of stem cell therapy and but

at the same time emphasizes the current state of high unpredictability with regards to in vivo cell therapy in humans.

Insofar as the extrapolation of results from the animal model to the human model, prior Art teaches that the conditions of a particular disease in an animal model may not correspond with the human condition. For example, mice with mutations in the cystofibrosis gene do not exhibit the pulmonary effects of cystic fibrosis seen in man, but rather suffer from severe gastrointestinal obstruction (Orkin et al., Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, December 7, 1995, p.11 paragraph. 3). Thus, the relevance of animal models for prevention of human neurodegenerative diseases may be compromised by phenotypical difference between the human patient and animal models of the disease. Thus, the state of prior Art teaches a lack of nexus between animal models to the human model.

In regards to the method of differentiating any species of MCS cells, which would encompasss human cells, wherein the MSC cells are exposed to any condition such that the said cells differentiate into neurons or oligodendrocytes. The state of the prior art, at time of filing, considered the culturing of bone marrow stromal cells or mesenchymal stromal cells (especially those derived from human) using any type of media or condition is unpredictable since the using "human stem cells are proving decidedly less predictable" Vogel et al. (Science Vol 290 p.1672). The use of any media or condition or culturing protocol would place undue experimentation on one ordinary skilled in the art since Applicant states "there was no indication that MSCs could differentiate into oligodendrocytes of neurons" (see p. 4 [0011]).

Hence, one skill in the Art at the time of the invention could not reasonably predict the method of providing MSC cells or oligodendrocytes precursor cells wherein the said cells were differentiated in vitro into neurons and oligodendrocytes and introducing said differentiated cells to the CNS of subjects for treatment of pathologies related to neurological disease whereby the differentiated cells will compensate for damaged myelin or neurological deterioration.

The predictability or lack thereof in the art/level of skill in the art

The predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. In view of the unpredictability that exist in the art, the relative skill of those in the art is considered to be relatively high at the time of the invention was made.

Guidance in the Specification and working examples

Analysis of Quantity of Experimentation

The specifications teach the preparation/isolation of MSCs from the rat and human bone marrow. The specification teaches about the immortalized cultures of MSCs differentiating into oligodendrocytes using B104 conditioned medium (Example 1 and 2 p. 25). The specification further teaches the administration of culture human MSCs into rats where cells are infected with a virus that expressed bacterial Lac Z and green fluorescent protein (GFP). The specification

describes that cells are integrated into the nervous system and states that Applicants observed no sign of immune rejection of administered cells (Example 3, page 26). The specification also describes the administration of MCS cell into lateral ventricles of myelin deficient newborn rats were observed to have differentiated into oligodendrocytes and neurons (Example 4 and 5, p.26-27). The specification teaches that rat MSCs, infected by retroviral infection with hTERT, are able to express exogenous hTERT gene (Example 5, p. 27). However, the instant claims are not enabled because the specification failed to demonstrate that the differentiated cell compensates for the said damaged myelin or neurological deterioration in the said subject suffering from said pathology. Moreover, the specification states that there are various stage-specific markers which be used to identify the known stages of oligodendrocyte development (see p. 19 last ¶) and states the mature oligoendrocytes develop with the regulated expression of markers such as proteolipid protein (PLP), myelin basic protein (MBP), and myelin/oligodendrocyte glycoprotein (MOG) (see p. 20 last ¶). However, Applicant did not demonstrate the use all of these markers in Example 4 p. 26. Instead, Applicant stated that "it was apparent that some myelin was present in the MD rats" and that indirect immunofluorescence analysis revealed the expression of PLP" consisting with the notion that human MSCs differentiated into oligodendrocytes. However, in the view of the unpredictability of the prior art regarding useable stem cell source especially human stem cells for cell therapies and in view of Castro et al (Science 2002 vol 297 p.1299) that teaches "bone to brain" trans differentiation may not be a general phenomenon but may depend on the experimental system in which the hypothesis is tested and in this particular case, bone marrow cells failed to transdifferentiate into neural cell in vivo (Table 1 p. 1299), it would be highly unpredictable that MSC would successful differentiate into neurons and

oliogodendrocytes such that compensation for myelin damaged or neurological deterioration would occur in vivo even in animal systems such as the rat model. Therefore, in light of the unpredictability of the prior art and lack of substantial data that MSC differentiated in the rats (as shown in Example 4) in such that the said cells compensated for the myelin damage or neurological damage, the invention commensurate of the claims is not enabled.

Lastly, applicant is silent about any factual data of any method of administering differentiated MCSs or oligodendrocytes precursor to any other subject other than rats to prevent neurodegenerative diseases. As such, the disclosed claims are very broad and are not enabled because the specification fails to teach a protocol to deliver effective amount of MSCs composition in all the subjects other than rat as claims are directed to a subject. Applicants have not provided guidance in the specification toward specific therapy treatment protocol, which would have avoid the many obstacles in utilizing MSCs to treat a patient where said patient has damaged myelin or neurological deterioration. Further, the specification does not provide any working example for "treating" a subject. With out guidance from the specification or the prior art, empirical experimentation would be required to determine an effective amount to treat a damaged myelin or neurological deterioration varying in the case of different diseases like Parkinson's disease, Alzheimer's disease, and stroke, as well as head trauma, or by dysfunction in ganglioside storage or demyelinization, such Tay-Sachs disease, G1 gangliosidosis, metachromatic leukodystrophy, and multiple sclerosis.

To attempt to practice the claimed invention, one ordinary skilled in the art would turn to the specification for guidance in practicing the invention. As set above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the

art. Another source of guidance for one skilled in the art, the prior art, again for reasons set forth above, also lacks solutions to overcome the considerable list of obstacles recognized in the field. In the absence of working examples from the specification and the prior art, one ordinary skilled in the art would resort to experimentation to navigate the obstacle to practicing the claimed invention. The totality of the cited references and the in view of the state of the art, at the time of filing, the solutions of these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art. In view of such unpredictability, more experimentation is warranted although no true expectation for success. The amount of experimentation required to practice the claimed invention would necessitate undue experimentation on the part of one ordinary skilled in the art. Also, animal models are valuable to test the concept from therapeutic point of view, however, as established above animal models do not mimic relevant human conditions and the translation of animal models success to human application is still unpredictable. Thus, the relevance of animal models to human therapy is not certain in most instances.

In conclusion, given the nature of the invention, state of the art, the lack of predictability found in the art, the breadth of the claims, the amount of guidance set forth in the specification, and the working example set forth it is concluded that the amount of experimentation necessary to practice the invention is very high and is in fact undue.

Claim Rejections - 35 USC § 102

A person shall be entitle to a patent unless-

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19-21 are rejected under 35 U.C.S 102(b) as being clearly anticipated by Roecklein et al (1995) Blood 85, no. 4 p. 997-1005.

Claims 19-21 are drawn to compositions that consist essentially of immortalized mesenchymal stromal cells and a physiologically acceptable carrier, and an exogenous gene. Roecklein teaches the cells with HPV E6/E7 genes (see p. 999, 1st column, 4th ¶, lines 4-7). Roeklein teaches the tranduced cells in culture which is a composition comprised essentially of cells and a physiologically acceptable carrier, that is media (p. 999, 1st column, 4th ¶, lines 10-14). Thus Roecklin clearly anticipates the claimed invention.

Conclusion

Claims 15-24 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malou C. Gemeniano whose telephone number is 571-272-6451. The examiner can normally be reached on 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER